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Revisión | Review

Anti-fertility and other biological activities of zoapatle (*Montanoa spp*.) with biotechnological application

[Anti-fertilidad y otras actividades biológicas del zoapatle (*Montanoa spp*.) con aplicación biotecnológica]

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Abstract: Species from the *Montanoa* genus have been used for hundreds of years in Mexican traditional medicine. The Náhuatl name given by Aztecs to this plant was "cihuapahtli", meaning "woman's medicine" (cihua, woman; pahtli, medicine), because *M. tomentosa* has been used to treat female health disorders since pre-Hispanic times due to its uterotonic properties. Later on, the Spanish pronunciation transformed the word into "zoapatle", the name still used by herb sellers in México. Despite its use in folk medicine, intensive scientific research on this plant did not begin until the early 1970's. The only two available reviews exclusively focused on the *Montanoa* species cover the period from 1529 to 1985. However, in the last two decades, important phytochemical, biochemical and biotechnological advances were achieved. This is a review of the history, botany, most relevant chemistry, biological activity and biotechnology of the secondary metabolites from the *Montanoa* genus so far.

Keywords: Ethnobotany, terpenoids, flavonoids, biological-activity, *Montanoa spp*.

Resumen: Especies del género *Montanoa* han sido empleadas por siglos en la medicina tradicional Mexicana. El nombre asignado a esta planta por los Aztecas fue "cihuapahtli", ó "medicina para la mujer" (cihua, mujer; pahtli, medicina). Específicamente, *M. tomentosa* es usada para tratar desordenes de la mujer desde tiempos prehispánicos por sus propiedades uterotónicas. La castellanización transformó esta palabra en "zoapatle", este nombre sigue siendo usado por los curanderos en México. A pesar de su uso en la medicina folklórica, la investigación científica intensa en esta planta comenzó desde inicios de 1970. Las únicas dos revisiones disponibles y dedicadas exclusivamente a las especies de *Montanoa* cubren el periodo de 1529 a 1985. Sin embargo, en las últimas dos décadas, se han logrado importantes avances fitoquímicos, bioquímicos y biotecnológicos. Este trabajo presenta una revisión de la historia, botánica, química más relevante, actividades biológicas y biotecnología de los metabolitos secundarios del género *Montanoa* a la fecha.

Palabras clave: Etnobotánica, terpenoides, flavonoides, actividad-biólogica, *Montanoa spp*.

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Occurrence, botanical description and ethnopharmacological background

The *Montanoa* Cerv. genus belongs to the Asteraceae family within the *Heliantheae* tribe. This group is widely distributed in México and has also been found in Central America. Most of the known Mexican species are located in the states of Guanajuato, Guerrero, Hidalgo, Estado de México, Michoacán, Morelos, Nayarit, Nuevo León, Oaxaca, Puebla, Querétaro, San Luis Potosí, Tamaulipas, Tlaxcala and Veracruz (Plovanich & Panero, 2004). The botanist Vicente Cervantes named this genus *Montanoa* to honor Luis José Montaña (1775 - 1820), a prestigious medical doctor who used this plant to treat humans (Gallegos, 1983). Searches for members of the Asteraceae family and *Montanoa* genus in the International Plant Names Index revealed 185 records, including 77 species (Appendix A) The morphological characterizations of the *Montanoa* spp. include capitula or heads with strongly conduplicate receptacular bracts and opposite, dentate and trinerve leaves. Common characteristics for the genus are sterile white ligules, white to yellow or, rarely, gray-black disc corollas, and accrescent pales that continue to grow and expand after anthesis, turning the flowering head into a spiny fruiting ball (Plovanich & Panero, 2004). Most species appear to flourish at relatively high elevations (1,650 to 2,500 meters above sea level) where the climate range is temperate (0 to 35 °C). Although a chromosome number of X=19 is common, some polyploidy was reported for some species (Funk & Raven, 1980). The accompanying vegetation consists primarily of cacti, yuccas and other small shrubs (Levine *et al.*, 1981). Plovanich & Panero (2004), detailed the phylogeny of 25 *Montanoa* species based on molecular markers. Their study contributed to a more accurate understanding of the phylogenetic relationships among *Montanoa* spp. within the *Heliantheae* tribe and complemented the previous morphological classification made (Funk, 1982).

Historically, the medicinal use of *Montanoa* spp. comes from Aztec healers who originally referred to this plant as "cihuapatli", meaning "woman's medicine" in Náhuatl (Alfaro, 1866). Due to Spanish influence, the word transformed into its current name of "zoapatle". According to old pre-Hispanic documents from the Aztecs, such as the "Florentine" and "de la Cruz-Badiano" codices, healers administered aqueous infusions of zoapatle to ease childbirth labor and to regulate the menstrual cycle in women (Lozoya, 1990). Ancient knowledge of zoapatle and other Mexican medicinal plants that were used as remedies for many disorders was first described in the "de la Cruz-Badiano codex" written in 1552, just 50 years after the Spanish conquest of Tenochtitlan. This codex was lost for 377 years, until 1929, when it was found in the Vatican library. Pope John Paul II returned it to México on July 19, 1990, 438 years after it was written. It is considered to be one of the most valuable documents of Aztec culture. It has not yet been totally deciphered, but active pharmacological properties have already been demonstrated for a dozen of the pre-Hispanic plants described. Among the most notable are the cihuapatli (*Montanoa*), some psychotropic plants like peyote (*Lophophora*) and toloache (*Datura*), the anti-parasitic plant epazote (*Chenopodium*), and yolloxóchitl (*Talauma*), which has cardiotonic effects. It was written in Náhuatl by the Aztec medical doctor Martín de la Cruz, translated into Latin by Juan Badiano from Xochimilco, México and beautifully illustrated by tlacuilos (painters). It is the oldest medical document from the Americas. On the first page, the preface is dedicated to Francisco de Mendoza, formal son of Don Antonio de Mendoza, New Spain's first Viceroy, because he ordered the elaboration of the document as a gift to the King of Spain. The king, however, never learned of the document, and, somehow, it arrived in the library of Diego de Contavila, a pharmacist from Madrid who lived until the mid-seventeenth century, shown by the written phrase *ex-libris didaci Cortavila*, which appears under the Francisco de Mendoza dedication. Later on, the nephew of Pope Urban VIII, Cardinal Barberini (1567 - 1679) acquired the document as shown by the note *Barberini Latin 241*. The codex ended up in the Vatican library, where it was abandoned and completely ignored until 1929, when it was re-discovered by the Latin teacher Charles U. Clark. This document has information on approximately 251 plants, 185 of which are illustrated. It has 13 chapters describing, principally, plants, minerals and animal products used by natives to heal diseases and ailments, divided into chapters as follows: Chapter I: Head remedies; Chapter II: Eye remedies; Chapter III: Hearing remedies; Chapter IV: Flu and cold remedies; Chapter V: Tooth and throat remedies; Chapter VI: Mouth and neck remedies; Chapter VII: Chest and stomach remedies; Chapter VIII: Bladder, buttocks, knee and foot remedies; Chapter IX: Black blood, fever and burn remedies;

Chapter X: Fear remedies; Chapter XI: Labor, menstruation and lactation remedies; Chapter XII: Children's remedies; and Chapter XIII: Signs of impending death. The document finishes in folio 63 with the inscription: *In Tlaltelolco* (a place in México City) *in the Santa Cruz College, in the Santa María Magdalena fest and in the year of the reparation of the world of 1552* (Shein, 1993).

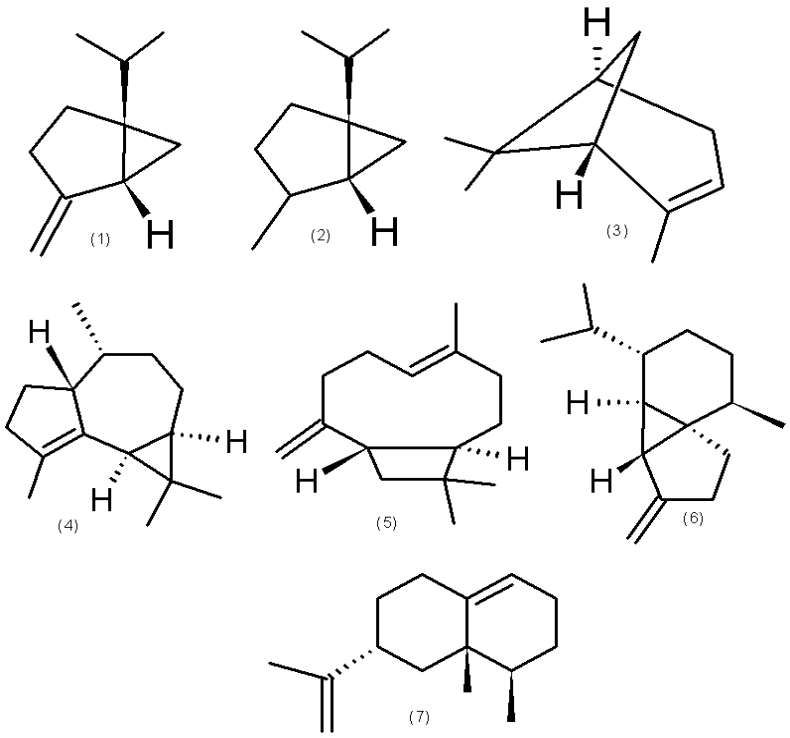

Figure 1
Main volatile organic compounds reported for some members of the *Montanoa* genus. Sabinene (1), α-thujene (2), α-pinene (3), α-gurjunene (4), β-caryophyllene (5), β-cubebene (6) and valencene (7).

The codex, and other similar documents, motivated scientific inquiry and led to the beginning of formal phytochemical research projects. The first project targeting zoapatle (Caballero & Walls, 1970), was done during the 1980's by the Mexican Institute for Social Security (IMSS), coupled with the General Coordination of the National Plan for Depressed Zones and Marginal Groups (COPLAMAR). They performed the most comprehensive ethnobotanical study ever conducted in México. The IMSS-COPLAMAR program gathered information including the types, names and formal medical descriptions of sicknesses; the plants and other natural products used by healers to prepare the appropriate remedies; and their use and application in rural communities across México (Lozoya-Legorreta *et al.*, 1988). Federal institutions were not alone in taking interest in the ancient patrimony of Mexican medicinal plants; private companies similarly considered the reports. The Ortho Corporation, which is owned by the Johnson & Johnson Company, began to focus on the *Montanoa* genus, particularly *Montanoa tomentosa*, the best-known representative from the genus, with an eye towards discovering new natural contraceptives. Of the 21 patents granted to the Ortho Corporation for the synthesis of single compounds and for the use of the decoction extract as a fertility control agent (Bejar *et al*., 2000), six patents (3,986,952, 3,996,132, 4,046,882, 4,060,604, 4,112,078, and 4,237,053) were acquired between 1976 and 1980 (Lozoya-Gloria, 2003).

From the early 1970's to the first decade of the twenty-first century, the *Montanoa* genus has been the subject of phytochemical, pharmacological,

molecular and biotechnological studies, demonstrating its relevance in natural product research and its potential application in the medical, industrial and agro-alimentary fields. These aspects will be reviewed later on.

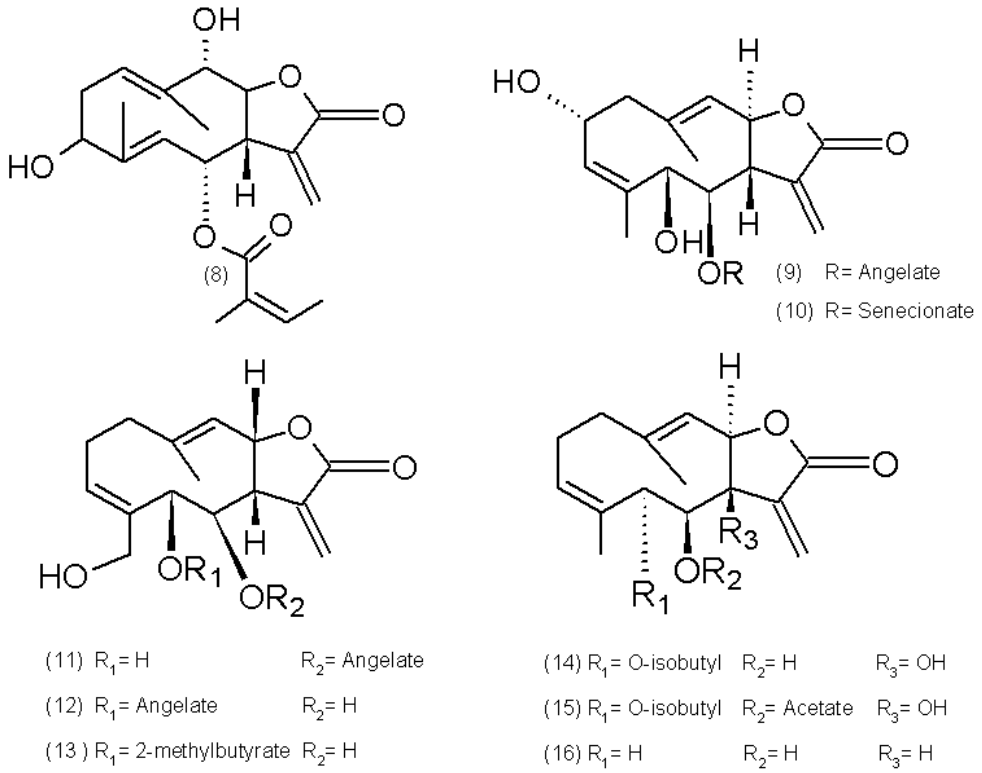

Figure 2
Representative germacradienolide sesquiterpene lactones from the *Montanoa* genus. Tomentosin (8), montafrusin A (9), montafrusin B (10), gigantanolides A (11), B (12) and C (13), leucanthanolide (14), leucanthanolide monoacetate (15) and 6-*epi*-deacetyllaurenobiolide (16).

Chemical composition

The most relevant compounds produced in *Montanoa* plants are terpenoids, mainly diterpenes but also including mono-, sesqui-, and triterpenoids as well as some interesting flavonoids. More than 70 compounds have been characterized from this genus so far, but fascinatingly, these compounds were indirectly identified in studies conducted to isolate the bioactive substances involved in the herb's uterotonic and contraceptive properties.

Monoterpenoids and sesquiterpenoids

Chemical profiles obtained by GC-MS and SPME-GC-MS (solid-phase microextraction-gas chromatography-mass spectrometry), revealed an abundance of monoterpenoids such as sabinene (1), α-thujene (2) and α-pinene (3) (Compadre *et al.*, 1987; Robles-Zepeda *et al.*, 2006). The most abundant sesquiterpenoids include α-gurjunene (4), β-caryophyllene (5), β-cubebene (6) and valencene (7) in volatile fractions from mesophyll and glandular trichomes of *M. tomentosa* (Robles-Zepeda *et al.*, 2009) (Figure 1). Over 20 sesquiterpene lactones were originally characterized in this plant group, however, their heterogeneous structure confines their possible use as chemotaxonomical markers of the genus.The first sequiterpene lactone isolated from the zoapatle aerial parts was tomentosin (8) in 1971 (Geissman and Griffin, 1971). Later on, the germacradienolide montafrusin A (9) and its analogue montafrusin B (10) were discovered in *M. frutescens* (Quijano *et al.*, 1979; Quijano *et al.*, 1986). New germacradienolide skeletons were also sought in less-studied species, such as *M. karwinskii* (Quijano *et al*., 1995) or *M. tomentosa* subsp. *xanthiifolia* (Lidia-Pérez *et al*., 1994), the most being discovered from *M. revealii, M. mollisima* (Seaman *et al.*, 1984a), *M. guatemalensis, M. tomentosa* subsp.

xanthiifolia (Castro & Jakupovic, 1985; Seaman *et al*., 1985), *M. atriplicifolia* (Bohlman *et al*., 1983), *M. dumicola* (Bohlman *et al*., 1984) and *M. grandiflora* (Quijano *et al*., 1984a). Representatives of germacradienolide-type compounds isolated from theses species include the gigantanolides A (11), B (12) and C (13), found in organic extracts of *M. gigas* (Quijano *et al*., 1987), as well as leucanthanolide (14) and leucanthanolide monoacetate (15) which along with 6-*epi*-deacetyllaurenobiolide (16), were present in aerial parts of *M. leucantha* and *M. hibiscifolia* (Oshima *et al*., 1986a) (Figure 2).

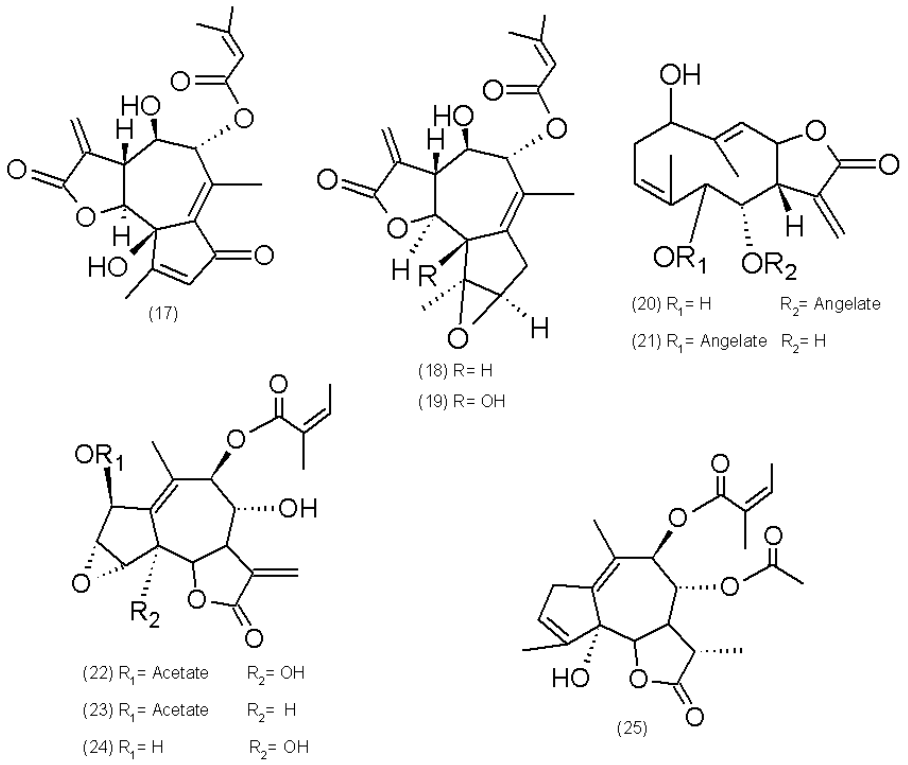

Figure 3
Heliangolide- and guaianolide-type sesquiterpene lactones from the *Montanoa* genus. Montacephalin (17), tomencephalin (18), 5-hydroxytomencephalin (19), and zoapatanolides A (20), B (21), C (22), D (23), E (24) and F (25).

Guaianolide and heliangolide sesquiterpene lactones were obtained from *M. tomentosa* subsp. *xanthiifolia* and *M. tomentosa* subsp. *rosei* (Seaman *et al*., 1984b), *M. tomentosa* subsp. *microcephala* (Topcu *et al*., 1988; Braca *et al*., 2001), and *M. imbricate* (Seaman *et al*., 1986). Montacephalin (17), tomencephalin (18), 5-hydroxytomencephalin (19) and zoapatanolides A (20), B (21), C (22), D (23), E (24) and F (25) (Quijano *et al*., 1982; Quijano *et al*., 1984b; Quijano *et al*., 1985a; Quijano *et al*., 1991a) are incorporated in this group (Figure 3). Eudesmanolide-type sesquiterpene lactones in this genus, consist of the montafrusins C (26), D (27), E (28), F (29) (Quijano *et al*., 1985b) and 1, 2-dehydro-3-oxocostic acid (30), (Seaman & Bencsath, 1985) from *M. frutescens* and *M. speciosa*, respectively. Novel members of this group were the dimeric eudesmanolide hydroxy-bis-dihydroencelin (31) (Quijano *et al*., 1991b), the antimycobacterial encelin (32), 1,2-dehydro-3-*epi*-isotelekin (33) (Sabanero *et al*., 1995), as well as unusual epoxyeudesmanolides with a rare endoperoxide structural element and rare carbonyl function such as 8α-(2',3'-epoxy-2'-methylbutyryloxy)-4 α-hydroxy-9-oxo-5*β*H-eudesm-1,11(13)-dien-6*β*,12-olide (34) (Müller *et al*., 2004) (Figure 4). Montahibisciolides probably are the most innovative sesquiterpene lactones isolated from the genus. In this group we could include (8α-Isobutyryloxy-9α-hydroxy-montahibisciolide (35); 8α-(2'-methylbutyryloxy)-9α-hydroxy-montahibis-ciolide (36); 8α-angeloyloxy-9α-hydroxy-montahi-

bisciolide (37); 8α-(2',3'-epoxy-2'-methylbutyryloxy)-9α-hydroxy-(11-13)-dehy-dromontahibisciolide (38) and 8α-(2',3'-epoxy-2'-methylbutyryloxy)-9α-hydroxy-1α-methoxy-1,10α-dihydromontahibisciolide) (39) which were originally found in *M. hibiscifolia* (Bohlmann *et al*., 1984) and *M. leucantha* (Quijano *et al*., 1994) (Figure 5).

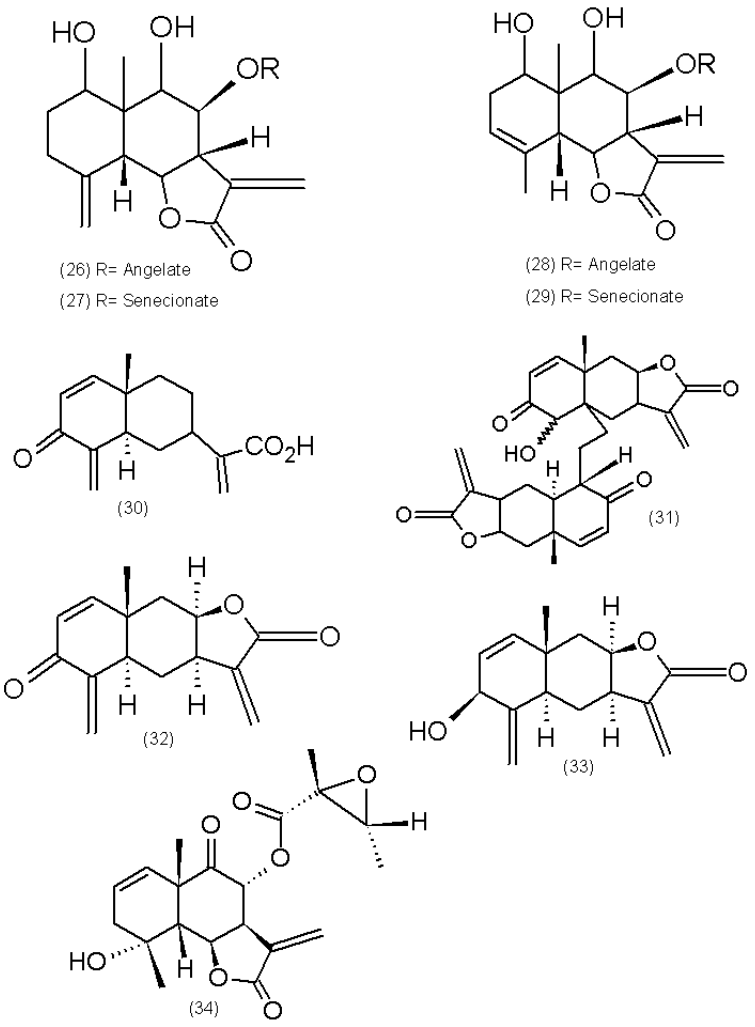

Figure 4
Representative eudesmanolide sesquiterpene lactones from the Montanoa genus. Montafrusins C (26), D (27), E (28), F (29); 1,2-dehydro-3-oxocostic acid (30), hydroxy-bis-dihydroencelin (31), encelin (32), 1,2-dehydro-3-*epi*-isotelekin (33) and 8α-(2',3'-epoxy-2'-methylbutyryloxy)-4α-hydroxy-9-*oxo*-5βH-eudesm-1, 11(13)-*dien*-6β,12-olide (34)

Diterpenoids

Zoapatanol (40) and montanol (41) were the first oxepane diterpenoids isolated from zoapatle in 1979 (Levine *et al*., 1979). Chemical analysis of the non-polar fraction of leaf extracts of *M. tomentosa* subsp. *tomentosa* lead to the isolation of tomexanthin (42) in 1984 (Seaman *et al*., 1984c), tomexanthol (43) in 1985 (Quijano *et al*., 1985c) and tomentanol (44) in 1986 (Oshima *et al*., 1986b). Minor quantities of 38 and 21-normontanol (45) were also discovered in organic extracts, but now, they are considered chemical artifacts produced from tomentol (46)

(Quijano *et al*.,1985c) and 40 (Marcelle *et al*., 1985), respectively. Pre-tomentol (47), pre-zoapatanol (48) and pre-tomexanthol (49) were also identified and later proposed to be the precursors of their respective final products (Quijano *et al*., 1985c) (Figure 6). In addition to this diterpenes synthetic derivatives with presumed contraceptive properties were developed (Taillier *et al*., 2004). The oxepane diterpenes have been detected only in *Montanoa* genus. This fact strongly suggests their specific biosynthesis in this genus, so they may be considered as taxonomical markers of this plant group.

Rigid tetracyclic diterpenoids are the most clinically studied compounds produced by these species. Kaurenal (50) (Castro & Jakupovic, 1985), kaurenoic acid (51) (Caballero & Walls, 1970), 16α-hydroxy-kaurenoic acid (52), 16α-hydroxy-kaurenoic acid methyl ester (53), (Campos-Bedolla *et al*., 1997) grandifloric acid (15α-hydroxy-kaurenoic acid) (54) (Campos-Bedolla *et al*., 1997), angeloyl grandifloric acid (55) (Quijano *et al*., 1994), cinnamoyl grandifloric acid (56) (Oshima *et al*., 1986a), grandiflorenic acid (57) (Caballero and Walls, 1970), 12-hydroxy-grandiflorenic acid (58) (Quijano *et al*., 1994), monoginoic acid (beyerenoic acid) (59), monoginol (60) (Gallegos, 1983) and the diterpene lactone zoapatlin (61) (Caballero & Walls, 1970) are considered valuable chemotaxonomical markers of both the *Montanoa* genus and the Asteraceae family (Figueiredo *et al*., 1995) (Figure 7). A synthetic derivative of 60, (±)-13-methoxy-15-oxozoapatlin (62), is the most well known antitumoral compound indirectly generated by the genus (Mi *et al*., 2002). More recently, evidence of non-early 13-hydroxylated gibberellins, such as GA_4 (63), was detected in young tissues of *M. tomentosa* plants (Villa-Ruano *et al*., 2009).

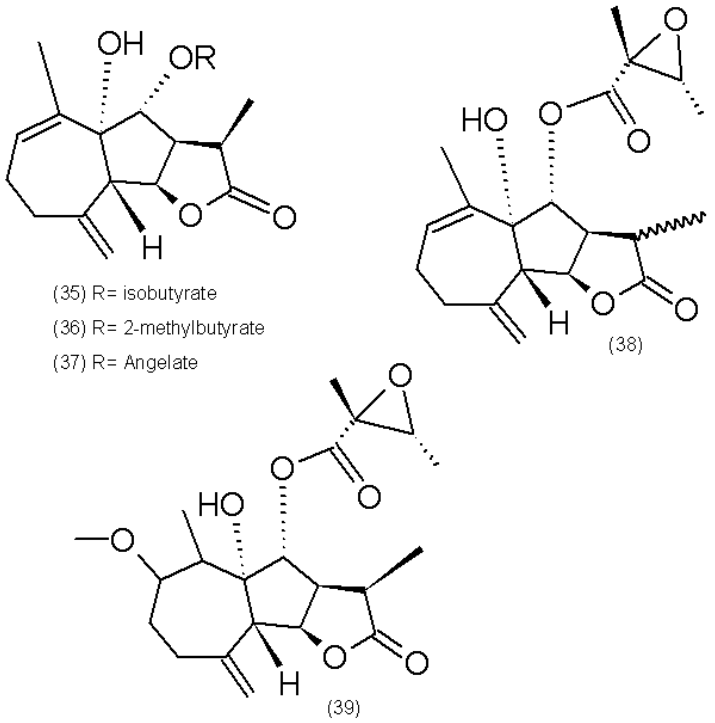

Figure 5
Some montahibisciolides isolated from the *Montanoa* genus. (8α-Isobutyryloxy)-9α-hydroxy-montahibisciolide (35), 8α-(2'-methylbutyryloxy)-9α-hydroxy-montahibisciolide (36), 8α-angeloyloxy-9α-hydroxy-montahibisciolide (37), 8α-(2',3'-epoxy-2'-methylbutyryloxy)-9α-hydroxy-(11-13)-dehydromontahibisciolide (38) and 8α-(2',3'-epoxy-2'-methylbutyryloxy)-9α-hydroxy-1α-methoxy-1,10α-dihydromontahibisciolide (39).

Triterpenoids

Non-polar extracts from *M. gigas* (Quijano *et al*., 1987), *M. leucantha* (Quijano *et al*., 1994), *M. tomentosa* subsp. *microcephala* (Topcu *et al*., 1988; Braca *et al*., 2001), *M. tomentosa* subsp. *xanthiifolia* (Lidia-Pérez *et al*., 1994), *M. karwinskii* (Quijano *et al*., 1995), *M. hibiscifolia* and *M. dumicola* (Bohlmann *et al*., 1984) lead indirectly to the identification and isolation of known triterpenes such as β-amyrin (64), β-amyrin acetate (65), stigmasterol (66), stigmasterol 3β-D-glucoside (67), β-sitosterol (68), taraxasterol (69), taraxasterol acetate (70), and lupeol (71) (Figure 8).

Flavonoids

MeOH extracts obtained from *M. tomentosa* subsp. *tomentosa* (Oshima *et al*., 1986c) and petrol extracts from *M. leucantha* (Quijano *et al*., 1994) contained the glucoside-flavonoids nicotiflorin (kaempferol 3-O-rutinoside) (72) and isoquercitrin (quercetin-3β-glucopyranoside) (73), and the aglycones 5,7,4'-trihydroxy flavone (74), 3,7,4'-trimethoxy-5-hydroxyflavone (75), 7,4'-dimethoxy-5-hydroxy-flavone (76), 6,7,4'-trimethoxy-5-hydroxyflavone (77) and 6,7,8,4'-tetramethoxy-5-hydroxyflavone (78) (Figure 9).

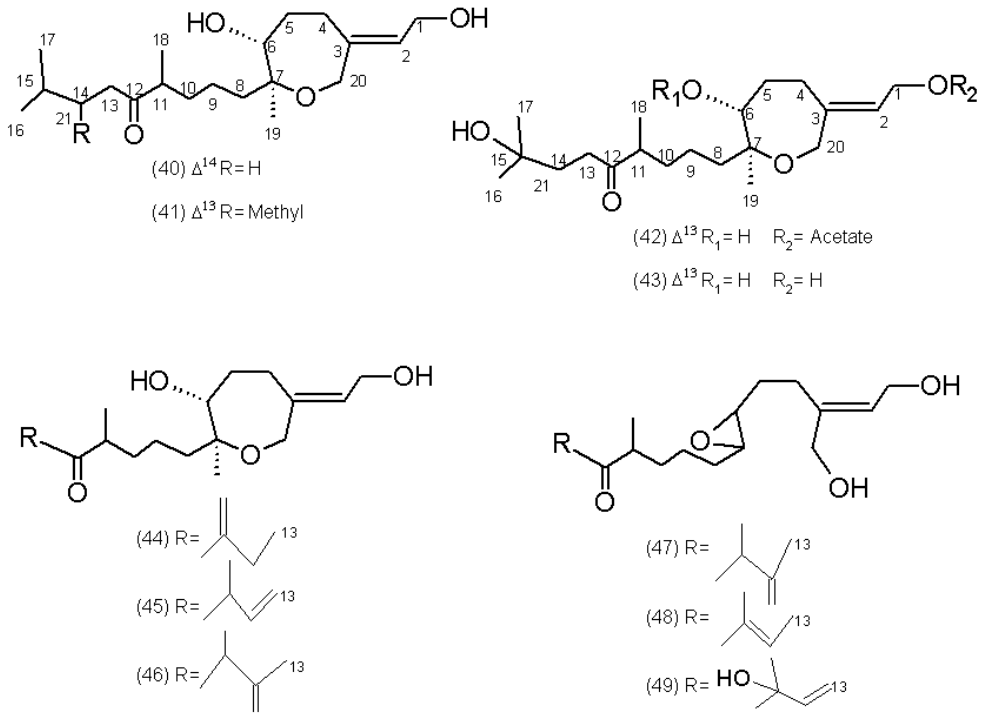

Figure 6
Oxepane diterpenes from the *Montanoa* genus. Zoapatanol (40), montanol (41), tomexanthin (42), tomexanthol (43), tomentanol (44), 21-normontanol (45), tomentol (46), pre-tomentol (47), pre-zoapatanol (48) and pre-tomexanthol (49).

BIOLOGICAL ACTIVITY

Sesquiterpenoids

Currently, 5 is an FDA (Food and Drug Administration) approved food additive, representing the first dietary cannabinoid, as a known ingredient in pepper-based condiments. Antitumor and anti-inflammatory effects have been reported for this compound (Gertsch *et al*., 2008).

Phytochemical research on the *Montanoa* genus has led to the discovery of a high number of these sesquiterpene lactones, but unfortunately, only a small percentage has been tested to determine their pharmacological or ecological properties. Although 8

was discovered in the early 1970's (Geissman & Griffin 1971), its antineoplastic and antifungal properties were only recently revealed (Cafarchia *et al*., 2001). Compound 14 has no uterotonic effect, but have cytotoxic activity in the *in vitro* KB and P-388 test systems (Oshima *et al*., 1986a). Compound 16 from *M. grandiflora* has shown promising effects against *Mycobacterium tuberculosis* at relatively low concentrations (16 µg mL^{-1}) (Cantrell *et al*., 2001). The guaianolides 17, 18, and 19, exhibit cytotoxic activity in the P-388 cell system (Topcu *et al*., 1988). The relationships in chemical structure between zoapatanolides (20-25) suggest that they could have analogous properties. To date, only compound 20 has been tested and found to be an inhibitor of uterine strips *in vitro*, nevertheless there is not any report on its presence in boiling aqueous solutions (Lu *et al*., 1987). Antimycobacterial activity has been assigned for some eudesmanolides such as (33) and (34), isolated from *M. speciosa* (Sabanero *et al*., 1995).

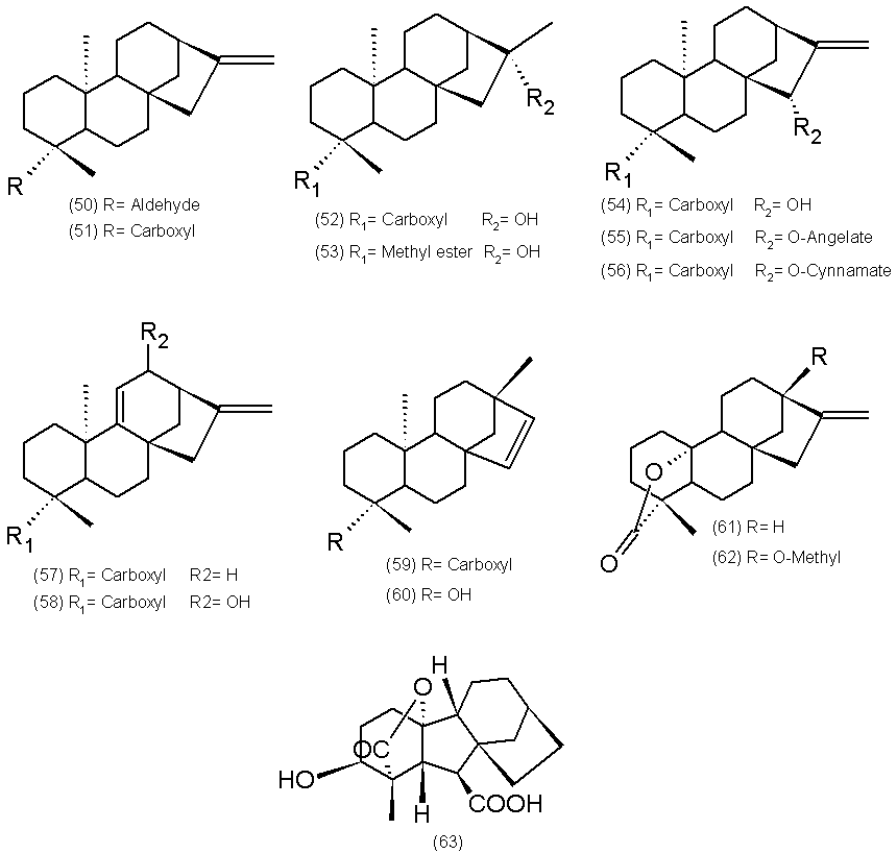

Figure 7
Tetracyclic diterpenes from the *Montanoa* genus. Kaurenal (50), kaurenoic acid (51), 16α-hydroxy-kaurenoic acid (52), 16α-hydroxy-kaurenoic acid methyl ester (53), grandifloric acid (15α-hydroxy-kaurenoic acid) (54), angeloyl grandifloric acid (55), cinnamoyl grandifloric acid (56), grandiflorenic acid (57), 12-hydroxy-grandiflorenic acid (58), monoginoic acid (beyerenoic acid) (59), monoginol (60), zoapatlin (61), (±)-13-methoxy-15-oxozoapatlin (62) and GA4 (63).

The montafrusins (26-29), which have the same skeleton type, and compound 30, have not been tested for this activity so far. 34 and similar compounds isolated from *M. hibiscifolia* showed effects on the inhibition of the transcription factor NF-κβ (nuclear factor kappa-light-chain-enhancer of activated B cells) (Müller *et al*., 2004). Likewise, montahibisciolides as 36 inhibited the NF-κβ transcription factor in Jurkat T and RAW 264.7 cells at low concentrations (10 µM) (Müller *et al*., 2004). Many other sesquiterpene lactones remain untested for biological activity, mainly because of their low endogenous concentrations, the availability of plant material year round, and a lack of improvements in extraction procedures (technical procedures). Unfortunately, many *in vitro* and especially, *in vivo* experiments using animal models require in many cases the order of grams to determine a possible biological activity. The dynamic biosynthesis of sesquiterpene lactones in the *Montanoa* genus predicts that interesting multifunctional enzymes that unluckily are still unknown could perform enzymatic reactions.

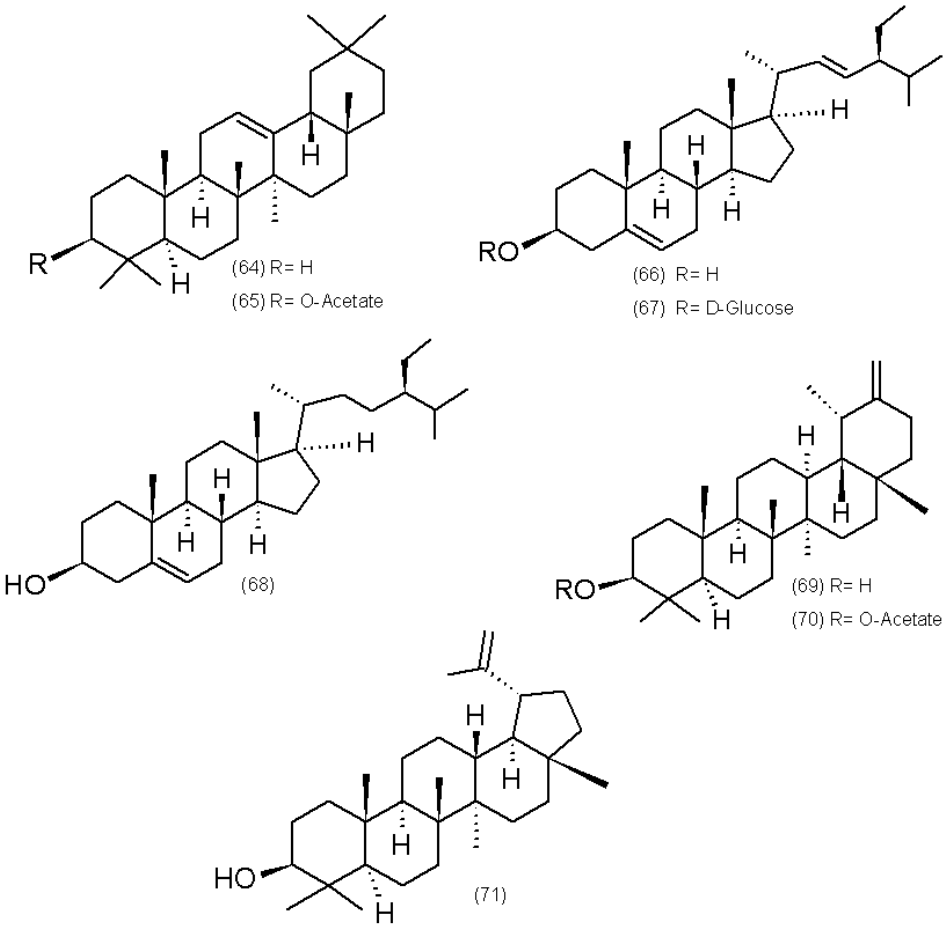

Figure 8
Triterpenoids and steroids from the *Montanoa* genus. β-amyrin (64), β-amyrin acetate (65), stigmasterol (66), stigmasterol 3β-D-glucoside, (68) β-sitosterol (67), taraxasterol (69), taraxasterol acetate (70) and lupeol (71).

Diterpenoids

40 were believed to be the only diterpenoid involved in the uterotonic effects of zoapatle´s aqueous crude extracts (ZACE). However, Smith *et al.* (1981), demonstrated that the individual use of 40 had no significant effect in *in vitro* systems for a variety of animal species. Ponce-Monter *et al*. (1983), and Lu *et al*. (1987), observed the same results for 40, 41 and

42. Only a synthetic analog of 40, called ORF 13811, was confirmed to have a potent anti-fertility activity when orally administered to guinea pigs and other animals (Hahn *et al*., 1984). Despite these findings, other works proposed that 40 was the compound associated to pregnancy interruption and that 41, 42 and 46 caused the inhibition of the spontaneous contraction of guinea pig uterine strips *in vitro* (Quijano *et al*., 1985c; Oshima *et al*., 1986b). Marcelle *et al*. (1985), demonstrated that free oxepane diterpenoids were sensitive to variations in light intensity and high temperature, causing alterations and even the complete destruction of their chemical structures. This study led to the development of efficient synthetic approaches to obtain oxepane diterpenoids, and modified derivatives, with anti-fertility properties (Hahn *et al*., 1984; Taillier *et al*., 2004). The controversial results on the uterotonic properties of oxepane diterpenoids published for different authors around the world, is not yet resolved. On the other hand, the results of these phytochemical studies revealed very high abundance (≥ 0.03% dry weight) of oxepane diterpenoids in *Montanoa* plants suggesting that they possess ecological functions, probably as anti-microbial or insecticidal agents. Nevertheless, these possible traits have to be further explored.

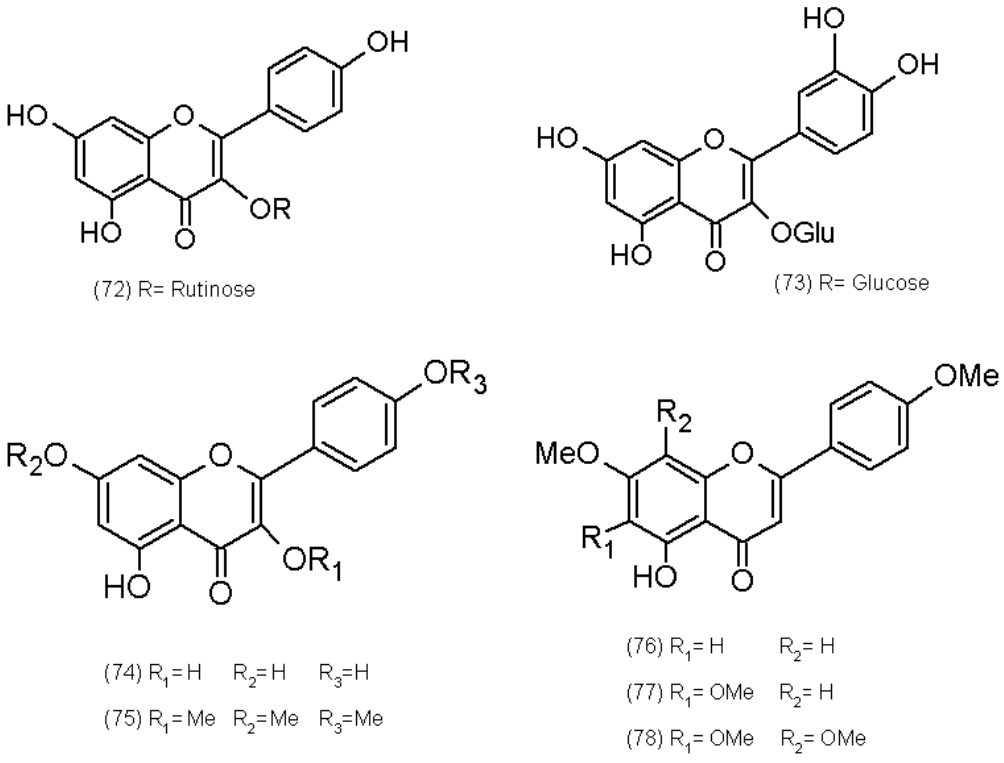

Figure 9
Flavonoids from the *Montanoa* genus. Nicotiflorin (kaempferol 3-O-rutinoside) (72), isoquercitrin (quercetin-3β-glucopyranoside) (73), 5,7,4'-trihydroxy flavone (74), 3,7,4'-trimethoxy-5-hydroxyflavone (75), 7,4'-dimethoxy-5-hydroxyflavone (76), 6,7,4'-trimethoxy-5-hydroxyflavone (77) and 6,7,8,4'-tetramethoxy-5-hydroxyflavone (78).

Ponce-Monter *et al*. (1983), reported that 51 and 57 (individually or mixed), reproduced the *in vitro* uterus contractility described by the oral administration of zoapatle decoctions. One year later, 57 was confirmed as a potent uterine muscle stimulant in rats (Bejar *et al*., 1984). Interestingly, the activity of both 51 and 57 was highly reproducible in rats, guinea pigs, dogs, hamsters, monkeys (baboons and rhesus) and, even, humans (Gallegos, 1985). Additionally, the effect of some kaurane derivatives

on human sperm motility was tested, but no significant effect was concluded (Valencia *et al*.,1986). Natural and synthetic kaurane-type diterpenoids were assayed, founding that 57 and its methyl ester induced uterine evacuation *in vivo* (Lu *et al*., 1987). Both 54 and 55 were found to be inhibitors of spontaneous uterine contractility (Lu *et al*., 1987; Campos-Bedolla *et al*., 1997). Compound 59 had no effect on rat uteri, but inhibited the electrically induced contraction of guinea-pig ilea (Zamilpa *et al*., 2002); however, spasmolytic as well as antimicrobial activities have been described for this diterpenoid (Zamilpa *et al*., 2002). Compounds 52 and 53 presented similar inhibition effects on the uterus contractility of guinea pigs and rats induced by oxytocin, as previously described for 54 (Ponce-Monter *et al*.,1988). The presence of 51, 57 and 59 in boiled decoctions was confirmed, demonstrating the high stability of the rigid tetracyclic diterpenoids, and providing scientific evidence on their involvement in the uterotonic phenomena described for ZACE in several animal species (Enríquez *et al*., 1996).

Compound 61 and synthetic derivatives such as 62 show potential as chemotherapeutic agents in HL-60, HUVEC (human umbilical vein endothelial cells), Ishikawa, KB, KB-V1, LNCaP, Lu1, MCF-7, Mel2, P-388, and SW626 cells (Mi *et al*., 2002). Natural occurring diterpenoids such as 51, 57 and their synthetic derivatives reveal a variety of effects as plant growth regulators and as antimicrobial, antiparasitic, insect antifeedant, cytotoxic, antitumor, anti-HIV, steroidogenic, antifertility, hypoglycemic, and embriotoxic agents (Ghisalberti, 1997; García *et al*., 2007). Despite kaurane-type diterpenoids are abundant in *Montanoa* plants, they are not exclusively limited in the genus, and other Asteraceae species actively produce this kind of molecules (García *et al*., 2007). Due to this fact, the botanical family represents in a general way a big source to obtain this diterpenoids.

Triterpenoids

Triterpenoids from *Montanoa* plants are associated with various pharmacological effects. Recently, the pentacyclic compounds 64 and 65 were found to possess antitubercular activity (Akihisa *et al*., 2005) and antifungal activity against *Candida albicans* (Johann *et al*., 2007). Compounds 64, 65 and 70 demonstrated anti-inflammatory effects in different animal models (Pinto *et al*., 2008) and 66 and 68 have shown antiviral activity (Khan *et al*., 1991). Phytosterols 67 and 68 decrease the risk of breast (Awad *et al*., 2000) and prostatic cancer (Wilt *et al*., 1999). Compound 71 induces apoptosis of human pancreatic adenocarcinoma cells via the Ras signaling pathway, and possesses anti-arthritic and anti-malarial properties (Murtaza *et al*., 2009). Compound 69 and similar triterpenes reduced cholesterol levels in humans; these molecules have been included as chemopreventive anti-cancer additives in dietary supplements (Ovesná *et al*., 2004). Compound 69 is an inhibitor of the oxidative decomposition of polyunsaturated fatty acyl chains involved in ~~some~~ human pathologi~~es~~y (Gallová *et al*., 2007). Triterpenes found in high concentrations in *Montanoa* are clearly related with the stability of plant cell membranes, chemical composition of leaf waxes, adaptation to different temperatures and plant defense (Dufourc, 2008).

Flavonoids

Compound 72 is a novel and efficient neuroprotectant that has been used as an efficient agent against permanent focal cerebral ischemia induced in rats (Runping *et al*., 2006); it also appears to improve memory and to counteract oxidative stress (Huang *et al*., 2007). Compound 73 is an effective eosinophilic inflammation suppressor and its use has been proposed for the treatment of allergies (Rogerio *et al*., 2007). Recently, this compound was associated with the reduction of glioblastomal cell proliferation (Amado *et al*., 2009). Compound 74, best known as apigenin, is a~~n~~ hypoglycemic agent and a strong inhibitor of Epstein-Barr virus (EBV) activation in Raji cells (Panda & Kar, 2007). Compound 76 is a key intermediary in the organic synthesis of robustaflavone, an anti-hepatitis B agent (Zembower & Zhang, 1998; Mooi *et al*., 2003).

Biotechnology of M. tomentosa

Volatile compounds identified in the *Montanoa* genus represent a rich source for industrial products because the essential oil of these plants contains high concentrations of 1, 2, 3 and 4. Compound 2 is the typical starting material from which 1-hydrate, a useful flavor component, is prepared. To prepare 2, 1 is isomerized in the presence of ethylenediaminolithium. Volatiles 1, 2 and 4 are used in the creation and/or manufacturing of a diverse amount of exotic fragrances and flavor concentrates (Ferro & Naves, 1974). Compound 3 is commonly used as flavoring agent for baked goods and is also a

common cosmetic ingredient. The use of 3 and 6 is approved for use in tobacco products as an additive or flavoring in several countries with Tobacco Product Regulations (Baker *et al*, 2004). Compound 7 is a commercially available and inexpensive sesquiterpene hydrocarbon that can be biotransformed into its ketonic derivative nootkatone, which is one of the most important and valuable compounds in the cosmetic and fiber sectors (Furusawa *et al*., 2005). Compound 74 is a yellow crystalline solid that has been used to dye wool.

Compounds 51, 57 and 59 have been the subjects of biotechnological research due to their biological activities. Undifferentiated callus from *M. tomentosa* leaves and cell cultures from those calluses, grown in the presence of 2,4-dichlorophenoxyacetic acid at 0.5 mg L^{-1} with kinetin at 2 mg L^{-1}, showed an increased accumulation of the three diterpenoids up to 2.1 mg g^{-1} dry weight in callus and up to 0.76 mg g^{-1} in cell suspension cultures (Villarreal *et al*., 2001). Studies on the biosynthesis of these diterpenoids revealed the activity of a putative microsomal *ent*-kaurenoic-C9 (11)-desaturase and a close relationship between 51 and 57 (Villa-Ruano *et al*., 2009). The biotransformation of 51 by *Rhizopus stolonifer* fungus produces a desaturated *ent*-kaurane 9(11) similar to 57 (Silva *et al.*, 1999), but this reaction had not been reported to occur in the plant itself until now. Involvement of 56 as precursor in the biosynthesis of physiologically active gibberellins (63 and GA_4-like compounds), and the transformation of *ent*-beyerene to 59 by a P450 oxidase achieved by experiments using ^{3}H-GGPP (geranylgeranyl-pyrophosphate) as a substrate, proposed alternative biosynthetic pathways (Villa-Ruano *et al*., 2009). Currently, the *M. tomentosa ent*-kaurene oxidase cDNA has been isolated (Villa-Ruano *et al*., 2010). The identification, molecular cloning and heterologous expression of the coding DNA sequences involved in the biosynthesis of sesquiterpene lactones and diterpenes represent a novel biotechnological method for scaling up their production (Ro *et al*., 2008).

CONCLUSIONS

Research efforts to find natural contraceptives in *Montanoa* resulted in the identification of over 70 compounds reported in the present review. Only some of these compounds showing pharmacological activities have recently been determined. The boiling aqueous solutions of *M. tomentosa* orally administered to induce childbirth, probably consist of a mix of different metabolites, but only the chemical stability of *ent*- kaurane diterpenoids was confirmed in these infusions (Enríquez *et al*., 1996). Therefore, this kind of diterpenoids should be strongly involved in zoapatle's uterotonic effects. *Montanoa* genus as many other Asteraceae plants biosynthesizes high amounts of sesquiterpene lactones, nonetheless just a few showed relevant biological activities. Unusual diterpenes, such as 40 and 61, were first characterized in this genus and now these molecules constitute classic models of organic synthesis (Taillier *et al*., 2004) . Besides the sesqui- and diterpenes reported in zoapatle plants and their controversies regarding pharmacological activities (Rios *et al*., 2012), here we present other natural products biologically active like triterpenoids and flavonoids with putative biotechnological potential. Today the *Montanoa* genus is not only important in reproductive medicine, but its relevance has been extended to other areas of experimental biology such as cancer, immunological, pathological, and biotechnological research. However, there are still many other research areas to be developed. The specific action mechanisms and receptors for kaurenes in the smooth muscle of female mammals, as well as their effects in other physiological targets are still unknown. Although they have similar effects as the oxytocin peptide, their mechanisms seem to be quite different. Also, a report of *M. tomentosa* extract having aphrodisiac effects on male was published, but no more information on the putative active compounds involved in this activity has been reported since 2006 (Carro-Juárez *et al*., 2006). Because of these reasons, zoapatle species have a privileged place among the medicinal plants of México and Central America.

Currently, the time required from initial clinical trials to FDA approval of a drug varies from 6 - 11 years, and it can take 1 - 2 years more to receive the final decision at a cost of about $125 million (Selected Regulations and Guidance for Drug Studies, 2011). Active *Montanoa* compounds have been used in humans for more than 200 years. However, other plant preparations have also been used, such as those illustrated in the Tepantitla mural found in Teothihuacán, the famous archaeological site just 30 miles northeast of México City. This site is believed to have been established around 100 BC. Some of the described plants have been used for more than 450 years in human beings (Ortiz de

Montellano, 1981). Ancient documents therefore represent a potentially rich information source for new medicinal natural substances.

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Appendix A

Records of Asteraceae family, *Montanoa* genus in the International Plant Names Index.

Id	Version	Family	Genus	Authors
136606-3	1.1	A	*M.*	Cerv.
10111-1	1.3	A	*M.*	Cerv.
894068-1	1.3	A	*M. ser. Amoenae*	V.A.Funk
894069-1	1.3	A	*M. ser. Apertae*	V.A.Funk
894070-1	1.3	A	*M. sect. Echinocephalae*	V.A.Funk
894071-1	1.3	A	*M. ser. Frutescentes*	V.A.Funk
894072-1	1.3	A	*M. ser. Grandiflorae*	V.A.Funk
894073-1	1.3	A	*M. ser. Hibiscifoliae*	V.A.Funk
894074-1	1.3	A	*M. ser. Intermediae*	V.A.Funk
894075-1	1.3	A	*M. ser. Ovalifoliae*	V.A.Funk
894076-1	1.3	A	*M. ser. Quadrangulares*	V.A.Funk
163981-2	1.2	A	*M. affinis*	S.F.Blake
233552-1	1.3	A	*M. affinis*	S.F.Blake
233553-1	1.3	A	*M. andersonii*	McVaugh
163982-2	1.2	A	*M. andersonii*	McVaugh
163983-2	1.2	A	*M. angulata*	V.M.Badillo
233554-1	1.1.2.1.1.1	A	*M. angulata*	V.M.Badillo
233555-1	1.4	A	*M. anomala*	B.L.Rob. & Greenm.
163984-2	1.1.2.1.1.1	A	*M. anomala*	B.L.Rob. & Greenm.
281019-2	1.3	A	*M. arborescens*	DC.
163985-2	1.3	A	*M. arborescens*	DC.
233556-1	1.1.2.1	A	*M. arborescens*	K.Koch
163986-2	1.2	A	*M. arsenei*	S.F.Blake
233557-1	1.3	A	*M. arsenei*	S.F.Blake
233558-1	1.1.2.2.1.1	A	*M. aschenbornii*	Sch.Bip. ex K.Koch
163987-2	1.2	A	*M. aschenbornii*	Sch.Bip.
233559-1	1.1.2.1	A	*M. atriplicifolia*	K.Koch
163988-2	1.2	A	*M. atriplicifolia*	Sch.Bip.
233560-1	1.3	A	*M. auriculata*	Cuatrec.
163989-2	1.2	A	*M. auriculata*	Cuatrec.
136630-3	1.2	A	*M. bipinnatifida*	(Kunth) K.Koch
233561-1	1.1.2.1	A	*M. bipinnatifida*	K.Koch
233562-1	1.1.2.1.1.1	A	*M. clematidea*	Hemsl.
163971-2	1.2	A	*M. clematidea*	Walp.
233563-1	1.1.2.2.1.1	A	*M. crenata*	Sch.Bip. ex K.Koch
163990-2	1.2	A	*M. crenata*	Sch.Bip.
233564-1	1.5	A	*M. dumicola*	Klatt ex T.Durand & Pitt.
163991-2	1.2	A	*M. dumicola*	Klatt
163992-2	1.2	A	*M. echinacea*	S.F.Blake
233565-1	1.1.2.2	A	*M. echinacea*	S.F.Blake
1167666-2	1.2	A	*M. elegans*	C.Koch
233566-1	1.1.2.1	A	*M. elegans*	K.Koch
163993-2	1.2	A	*M. elegans*	K.Koch
163972-2	1.2	A	*M. ensifolia*	Sch.Bip.
233567-1	1.1.2.1	A	*M. floribunda*	K.Koch
163994-2	1.2	A	*M. fragrans*	V.M.Badillo
233568-1	1.4	A	*M. fragrans*	V.M.Badillo

233569-1	**1.1.2.1.1.1**	**A**	***M. frutescens***	**Hemsl.**
163995-2	**1.4**	**A**	***M. frutescens***	**Mairet ex DC.**
233570-1	**1.1.2.1.1.2**	**A**	***M. gentryi***	**S.F.Blake**
163996-2	**1.2**	**A**	***M. gentryi***	**S.F.Blake**
163997-2	**1.2**	**A**	***M. gigas***	**Rzed.**
233571-1	**1.1.2.2.1.1**	**A**	***M. gigas***	**Rzed.**
163998-2	**1.2**	**A**	***M. gracilis***	**Sch.Bip.**
233572-1	**1.1.2.2.1.1**	**A**	***M. gracilis***	**Sch.Bip. ex K.Koch**
291565-2	**1.2**	**A**	***M. grandiflora***	**Benth.**
233574-1	**1.1.2.1.1.1**	**A**	***M. grandiflora***	**Hemsl.**
233573-1	**1.1.2.1.1.1**	**A**	***M. grandiflora***	**Hemsl.**
233575-1	**1.4**	**A**	***M. guatemalensis***	**B.L.Rob. & Greenm.**
163999-2	**1.1.2.1.1.1**	**A**	***M. guatemalensis***	**B.L.Rob. & Greenm.**
233576-1	**1.1.2.1.1.1**	**A**	***M. hemsleyana***	**S.F.Blake**
164000-2	**1.2**	**A**	***M. hemsleyana***	**S.F.Blake**
233577-1	**1.4**	**A**	***M. heracleifolia***	**Brongn.**
233578-1	**1.1.2.1.1.1**	**A**	***M. heterophylla***	**Hemsl.**
164001-2	**1.1.2.1.1.1**	**A**	***M. hexagona***	**B.L.Rob. & Greenm.**
233579-1	**1.4**	**A**	***M. hexagona***	**B.L.Rob. & Greenm.**
233580-1	**1.1.2.1**	**A**	***M. hibiscifolia***	**K.Koch**
163973-2	**1.4.2.1**	**A**	***M. hibiscifolia***	**Benth.**
164003-2	**1.3**	**A**	***M. hibiscifolia***	**(Benth.) D'Arcy**
233581-1	**1.4**	**A**	***M. hibiscifolia***	**(Benth.) D'Arcy**
164002-2	**1.4.2.1**	**A**	***M. hibiscifolia***	**Benth.**
136670-3	**1.1**	**A**	***M. hibiscifolia***	**K.Koch**
900321-1	**1.4**	**A**	***M. imbricata***	**V.A.Funk**
164004-2	**1.2**	**A**	***M. imbricata***	**V.A.Funk**
900322-1	**1.4**	**A**	***M. josei***	**V.A.Funk**
164005-2	**1.2**	**A**	***M. josei***	**V.A.Funk**
163974-2	**1.2**	**A**	***M. karvinskii***	**DC.**
233582-1	**1.1.2.1**	**A**	***M. karwinski***	**K.Koch**
164006-2	**1.2**	**A**	***M. laskowskii***	**McVaugh**
233583-1	**1.3**	**A**	***M. laskowskii***	**McVaugh**
164007-2	**1.2**	**A**	***M. lehmannii***	**S.F.Blake**
1085591-2	**1.1.1.2**	**A**	***M. lehmannii***	**(Hieron.) S.F.Blake**
233584-1	**1.1.2.1.1.1**	**A**	***M. lehmannii***	**S.F.Blake**
164008-2	**1.2**	**A**	***M. leucantha***	**S.F.Blake**
233585-1	**1.1.2.1.1.1**	**A**	***M. leucantha***	**S.F.Blake**
1034445-2	**1.3**	**A**	***M. leucantha***	**(Lag.) S.F.Blake**
954941-1	**1.2.2.1.1.1**	**A**	***M. leucantha var. arborescens***	**(DC.) B.L.Turner**
281020-2	**1.3**	**A**	***M. leucantha var. arborescens***	**(DC.) B.L.Turner**
921188-1	**1.5**	**A**	***M. leucantha subsp. arborescens***	**(DC.) V.A.Funk**
164009-2	**1.3**	**A**	***M. leucantha subsp. arborescens***	**(DC.) V.A.Funk**
164010-2	**1.2**	**A**	***M. liebmannii***	**S.F.Blake**
233586-1	**1.1.2.1.1.3**	**A**	***M. liebmannii***	**S.F.Blake**
233587-1	**1.4**	**A**	***M. macrolepis***	**B.L.Rob. & Greenm.**
164011-2	**1.1.2.1.1.1**	**A**	***M. macrolepis***	**B.L.Rob. & Greenm.**
233588-1	**1.1.2.2.1.1**	**A**	***M. microcephala***	**Sch.Bip. ex K.Koch**
164012-2	**1.2**	**A**	***M. microcephala***	**Sch.Bip.**
281021-2	**1.2**	**A**	***M. microcephala***	**Sch.Bip.**
164013-2	**1.2**	**A**	***M. mollissima***	**Brongn.**

233589-1	**1.4**	**A**	***M. mollissima***	**Brongn.**
1058190-2	**1.2**	**A**	***M. moritziana***	**Sch.Bip.**
164014-2	**1.4**	**A**	***M. moritziana***	**Sch.Bip. in Kuntze**
233590-1	**1.1.2.2.1.4**	**A**	***M. moritziana***	**Sch.Bip. Ex Kuntze**
233591-1	**1.4**	**A**	***M. myriocephala***	**B.L.Rob. & Greenm.**
164015-2	**1.1.2.1.1.1**	**A**	***M. myriocephala***	**B.L.Rob. & Greenm.**
164016-2	**1.2**	**A**	***M. olivae***	**Sch.Bip.**
233592-1	**1.1.2.2.1.1**	**A**	***M. olivae***	**Sch.Bip. ex K.Koch**
233593-1	**1.2**	**A**	***M. orbignyana***	**Klatt**
233594-1	**1.1.2.1**	**A**	***M. ovalifolia***	**K.Koch**
163975-2	**1.2**	**A**	***M. ovalifolia***	**DC.**
164017-2	**1.2**	**A**	***M. ovalifolia subsp. australis***	**V.A.Funk**
917115-1	**1.5**	**A**	***M. ovalifolia subsp. australis***	**V.A.Funk**
164018-2	**1.1.2.1**	**A**	***M. palmeri***	**Fernald**
233595-1	**1.3**	**A**	***M. palmeri***	**Fernald**
233596-1	**1.3**	**A**	***M. patens***	**A.Gray**
164019-2	**1.2**	**A**	***M. patens***	**A.Gray**
233597-1	**1.2**	**A**	***M. pauciflora***	**Klatt**
164020-2	**1.2**	**A**	***M. pauciflora***	**Klatt**
233598-1	**1.3**	**A**	***M. pilosipalea***	**S.F.Blake**
164021-2	**1.2**	**A**	***M. pilosipalea***	**S.F.Blake**
164022-2	**1.1.2.1.1.1**	**A**	***M. pittieri***	**B.L.Rob. & Greenm.**
233599-1	**1.4**	**A**	***M. pittieri***	**B.L.Rob. & Greenm.**
164023-2	**1.1.2.1.1.1**	**A**	***M. pringlei***	**B.L.Rob. & Greenm.**
233600-1	**1.4**	**A**	***M. pringlei***	**B.L.Rob. & Greenm.**
164024-2	**1.2**	**A**	***M. pteropoda***	**S.F.Blake**
233601-1	**1.3**	**A**	***M. pteropoda***	**S.F.Blake**
233602-1	**1.4**	**A**	***M. purpurascens***	**B.L.Rob. & Greenm.**
164025-2	**1.1.2.1.1.1**	**A**	***M. purpurascens***	**B.L.Rob. & Greenm.**
233603-1	**1.4**	**A**	***M. purpurea***	**Brongn.**
164026-2	**1.2**	**A**	***M. pyramidata***	**Sch.Bip.**
233604-1	**1.1.2.2.1.2**	**A**	***M. pyramidata***	**Sch.Bip. ex K.Koch**
233605-1	**1.1.2.2.1.1**	**A**	***M. quadrangularis***	**Sch.Bip. ex K.Koch**
164027-2	**1.2**	**A**	***M. rekoi***	**S.F.Blake**
233606-1	**1.3**	**A**	***M. rekoi***	**S.F.Blake**
233607-1	**1.1.2.2**	**A**	***M. revealii***	**H.Rob.**
164028-2	**1.2**	**A**	***M. revealii***	**H.Rob.**
233608-1	**1.4**	**A**	***M. rosei***	**B.L.Rob. & Greenm.**
164029-2	**1.1.2.1.1.1**	**A**	***M. rosei***	**B.L.Rob. & Greenm.**
164030-2	**1.2**	**A**	***M. samalensis***	**J.M.Coult.**
233609-1	**1.2**	**A**	***M. samalensis***	**Coult**
164031-2	**1.1.2.1.1.1**	**A**	***M. schottii***	**B.L.Rob. & Greenm.**
233610-1	**1.4**	**A**	***M. schottii***	**B.L.Rob. & Greenm.**
164032-2	**1.1.2.1.1.1**	**A**	***M. seleriana***	**B.L.Rob. & Greenm.**
233611-1	**1.4**	**A**	***M. seleriana***	**B.L.Rob. & Greenm.**
233612-1	**1.3**	**A**	***M. serrata***	**Rusby**
164033-2	**1.2**	**A**	***M. serrata***	**Rusby**
233613-1	**1.1.2.1**	**A**	***M. speciosa***	**K.Koch**
163976-2	**1.2**	**A**	***M. speciosa***	**DC.**
900323-1	**1.4**	**A**	***M. standleyi***	**V.A.Funk**
164034-2	**1.2**	**A**	***M. standleyi***	**V.A.Funk**

164035-2	1.2	A	*M. subglabra*	S.F.Blake
233614-1	1.3	A	*M. subglabra*	S.F.Blake
233615-1	1.4	A	*M. subtruncata*	A.Gray ex S.Watson
164036-2	1.2	A	*M. subtruncata*	A.Gray
164037-2	1.2	A	*M. tamayonis*	Aristeg.
233616-1	1.3	A	*M. tamayonis*	Aristeg.
164038-2	1.1.2.1	A	*M. tehuacana*	B.L.Rob.
233617-1	1.4	A	*M. tehuacana*	B.L.Rob.
233618-1	1.1.2.2.1.1	A	*M. ternifolia*	Sch.Bip. ex K.Koch
164039-2	1.2	A	*M. ternifolia*	Sch.Bip.
233619-1	1.1.2.1.1.3	A	*M. thomasii*	Klatt
233620-1	1.3	A	*M. tomentosa*	Cerv.
1183197-2	1.2	A	*M. tomentosa*	Cerv.
164040-2	1.1.2.1.1.1	A	*M. tomentosa*	Cerv.
163977-2	1.3	A	*M. tomentosa var. cordifolia*	DC.
921189-1	1.4	A	*M. tomentosa subsp. microcephala*	(Sch.Bip.) V.A.Funk
281023-2	1.3	A	*M. tomentosa var. microcephala*	(Sch.Bip.) B.L.Turner
164041-2	1.3	A	*M. tomentosa subsp. microcephala*	(Sch.Bip.) V.A.Funk
954940-1	1.1.2.1.1.4	A	*M. tomentosa var. microcephala*	(Sch.Bip.) B.L.Turner
921190-1	1.1.2.1.1.2	A	*M. tomentosa subsp. rosei*	(Rose ex Robinson & Greenm.) V.A.Funk
164042-2	1.1.2.1.1.2	A	*M. tomentosa subsp. rosei*	(B.L.Rob. & Greenm.) V.A.Funk
163978-2	1.3	A	*M. tomentosa var. ternifolia*	DC.
281022-2	1.3	A	*M. tomentosa var. xanthifolia*	(Sch.Bip.) B.L.Turner
954939-1	1.1.2.1.1.4	A	*M. tomentosa var. xanthifolia*	(Sch.Bip.) B.L.Turner
921191-1	1.4	A	*M. tomentosa subsp. xanthiifolia*	(Sch.Bip.) V.A.Funk
164043-2	1.3	A	*M. tomentosa subsp. xanthiifolia*	(Sch.Bip.) V.A.Funk
164044-2	1.2	A	*M. triloba*	Sch.Bip.
233621-1	1.1.2.2.1.1	A	*M. triloba*	Sch.Bip. ex K.Koch
163979-2	1.2	A	*M. trilobata*	Ram.Goyena
233622-1	1.1.2.2.1.1	A	*M. uncinata*	Sch.Bip. ex K.Koch
164045-2	1.2	A	*M. uncinata*	Sch.Bip.
233623-1	1.3	A	*M. wercklei*	A.Berger
164046-2	1.2	A	*M. wercklei*	A.Berger
233624-1	1.1.2.2.1.1	A	*M. xanthiifolia*	Sch.Bip. ex K.Koch
281024-2	1.2	A	*M. xanthiifolia*	Sch.Bip.
164047-2	1.2	A	*M. xanthiifolia*	Sch.Bip.

International Plant Names Index (http://www.ipni.org/index.html)
(A), Asteraceae; (M), *Montanoa*